

Annual Reporting Form for SCEDDBO Projects and Cores

Center Overview

Period covered by the report: 5/1/2011 – 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Marie Lynn Miranda, Allison Ashley Koch, Richard Auten, W. Michael Foster, Alan Gelfand, Pamela Maxson, Evan Myers, Jerome Reiter, Geeta Swamy, Redford Williams

Project Period: Year 5

Objectives of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO)

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes is to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center are:

1. *To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;*
2. *To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;*
3. *To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;*
4. *To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities; and,*
5. *To translate the results of the Center into direct interventions in clinical care and practice.*

SCEDDBO leverages and promotes active partnerships among the Nicholas School of the Environment, the Duke University Medical Center, Trinity College of Arts and Sciences, as well as the School of Natural Resources and Environment and the Children's Environmental Health Initiative at the University of Michigan and Durham County Public Health (DCPH) and the Lincoln Community Health Center (LCHC). The Center brings together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations.

Synthesis across SCEDDBO. Research Project A: Mapping Disparities in Birth Outcomes provides population-level research on health disparities in birth outcomes. Spatially-linking 1.7 million birth records with environmental, social, and host factor data layers allows for population-level analysis of potential co-factors identified in both the clinical obstetrics **Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes** and mouse model **Research Project C: Perinatal Environmental Exposure**

Disparity and Neonatal Respiratory Health studies. The data from Research Project A is spatially linked in GIS to the data from Research Project B.

The two neighborhood assessments (2008 and 2011) undertaken in Research Project B provide important neighborhood-level environmental and social data to Research Project A. In addition, the environmental data developed for Research Project A works synergistically with the mouse model work in Research Project C. For example, the air quality data from Research Project A is being used to further refine experimental dose design in Research Project C. In turn, results from Research Project C regarding experimental effects of multiple environmental agents on fetal growth restriction and postnatal somatic and lung development help point to locations in North Carolina where we are looking more closely at air quality impacts on birth outcomes in Research Project A.

Thus Research Project A is an epidemiological study, while Research Project B is a complementary clinical obstetrics project. Both projects focus on how combined environmental, social, and host factors shape disparities in birth outcomes. Research Project B also allows for additional host factor analysis. Research Project C uses a mouse model system to explore how disparities in exposure and response to exposure initiate and/or enhance disparities in birth outcomes and subsequent neonatal respiratory health. Like Research Projects A and B, Project C explores the effects of *combined* environmental exposures to prototypical air pollutants common in North Carolina (particulate matter and ozone) and non-chemical stressors on fetal growth restriction, neonatal somatic growth, and subsequent lung development and function.

The synergy among the research projects is facilitated by the GIS and Statistical Analysis (GISSA) Core. The GISSA Core allows for data analysis of the very large amount of data through the use of high-end GIS applications in combination with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, thus permitting multi-level analysis. Research Projects A and B both apply a Bayesian spatial hierarchical modeling approach to capture uncertainties in pregnancy outcomes and to elucidate the contributions of economic, sociocultural, and environmental stressors on health disparities in pregnancy outcomes. State-of-the-art GIS methods allow for sophisticated spatial statistical analyses at highly resolved spatial scales.

The GISSA Core also provides the analysis of the biological response and genetic data generated in Research Projects B and C. The rich source of social, environmental, and host data in Project B, coupled with sophisticated statistical genetic approaches for identifying gene-gene and gene-environment interactions, provides the opportunity to make important discoveries of how these higher order interactions may be working together to promote or prevent adverse birth outcomes. By serving as a central clearinghouse for statistical analysis, the GISSA Core tracks outcomes in each project and uses these discoveries to guide the analysis in each of the other projects.

The Community and Outreach Translation Core (COTC) facilitates the communication of findings from our large-scale study and future more-focused investigations. The COTC supported the implementation of the neighborhood assessment undertaken in Research Project B and continues to communicate the results of the assessment to community partners and stakeholders. In addition, the COTC draws on the GISSA Core to develop materials that communicate the results of the research projects in formats and applications that are immediately accessible to the lay public.

SCEDDBO is characterized by significant synergies among center components. To provide concrete examples of how the work of the center is moving forward in a collaborative way, here we highlight four areas: air pollution, social context of environmental stress, the Community Assessment Project, and statistical methods development. We provide summaries in this center overview; additional details can be found in the individual center component write-ups.

Air Pollution. To investigate the relationship of air pollution exposure and pregnancy outcomes, we have examined air pollution in all three projects. In Projects A and B, we have used criteria air pollutant data from the EPA AQS monitoring network, as well as CMAQ and FUSED modeling data. In addition, we are utilizing highly resolved air toxics data. These data have been spatially linked to the births in both Projects A and B. In addition, we have created a road proximity measure which can be used in both Projects A and B. The road proximity measures allow us to consider a relatively simple metric for assessing risk of exposure to air pollution, specifically traffic-related air pollution which includes particulate matter and diesel exhaust, both of which are being investigated within Project C.

The Social Context of Environmental Stress. We continue to work toward synthesis across all three projects. We have been able to combine our knowledge of the pregnant women in Project A with our rich data from the pregnant women in Project B. With our access to the North Carolina Detailed Birth Record (DBR) in Project A, we have been able to link participants in Project B with their birth certificate data. Using maternal and infant identifying information, including name, place, and date of birth, we have been able to link 1349 (99.0%) participants who completed the study and had a live birth by December 31, 2009 and 96 (79.3%) participants that were lost-to-follow-up but with an expected delivery date on or before December 31, 2009 (additional births will be linked as the DBR data become available). This linkage will allow us to examine multiple questions including racial residential segregation, residential mobility, and maternal medical complications. The rich psychosocial health data from Project B is being combined with the air pollution data from Project A to examine the combination of chemical and non-chemical stressors.

Additionally, the effects of resource deprivation suggested by findings in Projects A and B prompted Project C to add a resource deprivation (nesting restriction) component in order to test the proof-of-principle that the combination of multiple stressors/environmental contaminants may affect health even when the individual exposures do not.

Community Assessment Project/Built Environment. An important measure of potential environmental stress is the built environment. Our second wave of the Community Assessment Project assessed built environment variables for over 30,000 tax parcels, including the home addresses of 65% of the participants in Project B. Analyses of the built environment data continue, with publications in year 5 on the relationships between built environment and birth outcomes, psychosocial health, and pediatric obesity. Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency communities, census block group, census tract, and city-defined neighborhoods). The continuous and categorical scale variables have been merged with the Durham birth records (Project A) and with the clinical OB participants' records (Project B), which enables multiple analyses of the relationships among the built environment, psychosocial health, and pregnancy outcomes.

Statistical Methods Development. We continue two projects that capitalize on combining information in the data for Project A and Project B. The first project is to utilize the fine detail in Project B data to improve analyses involving Project A data.

The second project is to use the Project B data to check the sensitivity of conclusions from Project A analyses to potential unmeasured confounding. This is accomplished by comparing the findings from models fit using Project A data with the findings from parallel models fit using Project B data that control for additional relevant variables available only in Project B. If the associations found in the Project A models remain robust after including the potential confounders from Project B, our confidence in the conclusions increases. We are working on methods that perform such tests in a principled, model-based manner. In a related project, we also are checking the sensitivity of conclusions from Project A analyses to possible measurement errors in the data. For example, educational attainment variables for mothers in the intersection of Project A and Project B are quite different on the two datafiles. We treat Project B education values as truth—since we are more confident in their accuracy—and replace the Project A education values with this new truth. For mothers in the intersection of the datasets, we then can re-run analyses to see if results change dramatically. We also are working on imputing corrected values of education for the entire Project A data.

Administrative Core

Period covered by the report: 5/1/2011– 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Marie Lynn Miranda, Richard Auten, Pamela Maxson

Project Period: Year 5

Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, a Co-Director, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

- a. Provide scientific direction and leadership;
- b. Coordinate and foster interactions among research project and facility core investigators;
- c. Provide administrative services for the Center;
- d. Direct the Young Investigators program; and
- e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social, and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments

Quality Management Plan. The Administrative Core continued to distribute the Quality Management Plan (QMP) to all new SCEDDBO collaborators. These individuals are required to sign the cover sheet thereby agreeing to abide by the policies laid out in the QMP. The Administrative Core keeps a copy of these signed forms in its files. In year 5, the Administrative Core completed the internal audit on the participant data files for Project B: Healthy Pregnancy, Healthy Baby Study for quality assurance purposes.

Young Investigators Program. Richard Auten and Marie Lynn Miranda continue to mentor Geeta Swamy. Marie Lynn Miranda continues to serve as a mentor to Dr. Heather Stapleton and Dr. Rebecca Fry.

Year Five Expenditures. Year five expenditures matched projections in most areas. Spending on lab costs, particularly expanding the animal models, was higher than anticipated, largely due to the expansion to social stress models. Spending was slightly lower than budgeted for personnel costs due to personnel shifts that occurred throughout year five. We have been granted a no-cost extension, enabling us to continue our ongoing work.

IRB Certification. A centralized database on IRB and IACUC certification and continuing education requirements is maintained through the Administrative Core. Twice a year, Dr. Pamela Maxson, the QA Manager, verifies that all researchers associated with SCEDDBO have completed their basic certification and continuing education requirements (one credit of continuing education is required each year to maintain certification). Reminders are sent to investigators when they are due for additional training. In addition, Dr. Maxson is responsible for ensuring IRB and IACUC Protocols are renewed and updated as necessary. All of these documents are posted to the SCEDDBO internal website, and paper copies are centrally maintained by Dr. Maxson.

Meetings. The Executive Committee typically met monthly, in advance of the Internal Steering Committee meetings, in order to set the agenda for the larger monthly all-hands meetings. Subgroups met more frequently this year as we prepared for the submission of the renewal.

Website. The Administrative Core provided material on SCEDDBO to the EPA for uploading to the EPA children's centers website. In addition, we updated our SCEDDBO website, linked off the website for the Children's Environmental Health Initiative (cehi.snre.umich.edu). We continue to use our secure internal website that allows for discussion boards, email communication, and document storage associated with the work of each of the SCEDDBO components.

Dissemination. Numerous talks were given throughout the year by SCEDDBO investigators at a variety of different conferences as described in the research project write-ups below.

Training opportunities. We provided multiple training opportunities to SCEDDBO investigators and research staff. These opportunities included both intensive short course and semester long coursework for several research staff, as well as travel to professional meetings for researchers supported on the SCEDDBO grant.

New Collaborations. As part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we continue our collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Assistant Professor, Gillings Global School of Public Health, UNC. We

continue working with Dr. Bilbo on mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. We are working with Dr. Fry to explore gene expression and epigenetic changes associated with *in utero* metals exposures, with a particular emphasis on cadmium. In addition, we continue our CDC-funded collaboration with Dr. Heather Stapleton, Assistant Professor, Nicholas School of the Environment, Duke University. This study leverages our completed clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function. We have successfully sought and received funding from the NIH to support further development of this work. Multiple papers are in progress or have been published on this work in year 5.

Personnel. Year 5 brought the end of participant recruitment for Project B, ending our need for clinical recruiters.

National Service. Duke continues to organize and host the Children's Environmental Health Centers' monthly conference calls. In addition, Dr. Miranda continues to serve as a standing member of the Children's Health Protection Advisory Committee. Dr. Miranda completed her service on the NIH's Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions (IRAP) Study Section. Multiple SCEDDBO investigators help to review proposals for federal funding agencies, as well as review manuscripts for peer-reviewed journals.

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2011 – 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Pamela Maxson, Evan Myers

Project Period: Year 5

Objectives of Research

Project A utilizes the conceptual framework of the “weathering hypothesis,” which posits that chronic and persistent stressors lead to accelerated biological aging of women, which in turn accounts for adverse birth outcomes among certain subpopulations. The central objective is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than

- percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups.

Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has moved forward at small group level to discuss new research ideas, review progress of current analysis and identify next steps, and work on manuscript preparation.

A continuing goal is the linking of the detailed birth record data to USEPA PM₁₀, PM_{2.5}, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress has been made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone. A manuscript on this work appeared in the *Journal of Exposure Science and Environmental Epidemiology* (Gray et al., 2010). A critical issue in this work is addressing the misalignment between where monitoring stations are and where pregnant women live. Two approaches have been explored. One considers buffers of varying radii around monitoring sites to see how the exposure signal is affected by increasing distance from the site. The other attaches more uncertainty to the putative exposure as the distance from the monitoring site to the residence increases. Again, various exposure windows and metrics are considered. This work has appeared in *Statistics and Medicine* (Gray et al, 2011). Time-to-event investigation of the effect of particulate matter and birth outcomes has appeared in Chang et al. (2012a) and further study is forthcoming in Chang et al (2012b).

Related work has studied the use of a PM_{2.5} exposure simulator to explain birthweight. In a recently submitted paper, a template is developed for using an *environmental dose simulator* to connect ambient exposure to personal exposure. Then, using various exposure metrics, calculated from these personal exposures, which are clinically plausible over the course of a pregnancy, linkage is built to adverse birth outcomes. This work has appeared in *Environmetrics* (Berrocal et al., 2011).

Ongoing work has been devoted to a novel project concerned with connecting the *built environment* to adverse pregnancy outcomes. Built environment data has been collected under the Community Assessment Project and, after preliminary analysis has focused on spatial layers capturing four primary attributes of the built environment - housing damage, property disorder, tenure, and vacancy. Connection has been made to pre-term birth and low birth weight. Resultant work examining a bi-probit regression model as well as marginal logistic regressions has appeared (Miranda et al. 2012). Future work will move from binary to

continuous responses. Other work connecting the built environment with adverse birth outcomes appears in Miranda et al. (2012) and is forthcoming in Miranda et al. (2012b).

Our project on *racial residential segregation* has now seen the completion of one paper which enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we eventually decided that, given the significantly more detailed data available for Durham County, we would focus on this area to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences. A paper has now appeared in the journal *Spatial and Spatio-temporal Epidemiology* (Anthopolos et al., 2011).

Another component of our work has focused on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution. Such downscalers can be dynamic, enabling the tracking of exposure through time. With improved estimation of local exposure, we can better examine linkage between exposure and adverse birth outcomes. Three papers on this methodology have been completed. The first, for the univariate case, appeared in the Journal of Agricultural, Biological and Environmental Statistics (Berrocal et al, 2010). The second considers the bivariate problem, looking at downscaling two exposures (ozone and PM2.5), borrowing strength in the joint modeling. This work has appeared in the *Annals of Applied Statistics* (Berrocal et al. 2010). Most recent work has focused on measurement error associated with downscaling. Such error is attributable both to misalignment between monitoring sites and model grids as well as to effects of neighboring grids on local monitoring site levels. This work has appeared in *Biometrics* (Berrocal et al., 2012).

Another recently completed manuscript builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. Joint modeling eliminates potential causal inference concerns. A paper has appeared in *Statistics in Medicine* (Schwartz et al., 2011). Follow-on work extends this work to incorporate spatial structure, introducing spatial random effects in the regression modeling for both outcomes. This work has recently been submitted (Neelon et al. 2012).

We have also examined quantile regression methodology in explaining the effect of exposure on pregnancy outcomes. Here, the idea is that, rather than explaining mean birthweight as in customary regression models, we would be interested in explaining quantiles for birthweight. For instance, it would be of interest to explain the 10th percentile of birthweight since this is the threshold for declaring low birthweight. It emerges that risk factors and environmental exposure affects different quantiles differently. (See Lum and Gelfand 2012)

In addition, we have completed work on specific analysis and manuscripts examining the impact of maternal age and birth order on birth weight (*Journal of Epidemiology and Community Health*,

Swamy et al., 2011), on modeling ordinal categorical data using Gaussian processes (*Stochastic Modeling*, Heaton et al, 2011), on the etiology of racial disparities in maternal hypertensive disorders (*Public Health Reports*, Miranda et al., 2010), on maternal hypertension (Neelon et al. 2011, Vinikoor-Imler, 2012)

We have completed considerable methodological work on expected performance accruing to *synthesizing categorical datasets* with the objective of enhancing inference. We are particularly interested in how to deal with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap. This work attempts to synthesize cross classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. This is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table as well as for derived quantities such as relative risks and odds ratios. We have made substantial progress on the underlying modeling and have developed a simulation example as well. We have also addressed the issue of the complete dataset not being a random sample from the population, as would be typical in practice. A manuscript on this work has been revised and resubmitted. (See Berrocal et al., 2012)

Collaborations with other SCEDDBO Components

We continue our engagement with the other two research projects, as well as a strong connection with the GISSA and COTC.

Future Activities

Achieving a better understanding of exposure to air toxins, particularly particulate matter and ozone, is a central focus of our future efforts. Areas of investigation will include space time analysis of trends in births across North Carolina, an investigation of linked births (same mother) using suitable random effects models, and a more thorough investigation of the impact of introducing spatial random effects in regression modeling to explain birth outcomes.

We are continuing the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

We continue to target various professional audiences for dissemination of our work. Recent presentations have been at conferences under the auspices of the Joint Statistical Meetings, the American Public Health Association, the Society of Epidemiological Research, the International Biometric Society, and the Society of Maternal and Fetal Medicine.

Publications

Anthopolos, R., James, S.A., Gelfand, A.E., Miranda, M.L. 2011. "A Spatial Measure of Neighborhood-level Racial Isolation Applied to Low Birthweight, Preterm Birth, and Birthweight in North Carolina." *Spatial and Spatio Temporal Epidemiology*. 2(4): 235-246. PMID: 22748223.

Berrocal, V., Gelfand, A., Holland, D. 2012. "Space-time Data Fusion under Error in Computer Model Output: an Application to Air Model Quality." *Biometrics*. Forthcoming.

Berrocal, V.J., Gelfand, A.E., Holland, D.M., Burke, J., Miranda, M.L. 2011. "On the Use of a PM_{2.5} Exposure Simulator to Explain Birthweight." *Environmetrics*. 22(4), 553-571. PMCID: PMC3116241.

Chang H.H., Reich B.J., and Miranda M.L. "A Spatial Time-to-Event Approach for Estimating Associations between Air Pollution and Preterm Birth." *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. Forthcoming.

Chang, H.H., Reich, B.J., Miranda, M.L., 2012. "Time-to-Event Analysis of Fine Particle Air Pollution and Preterm Birth: Results from North Carolina, 2001-2005." *American Journal of Epidemiology*. 175(2): 91-98. PMID: 22167746.

Gray, S.C., Gelfand, A.E., Miranda, M.L. 2011. "Hierarchical Spatial Modeling of Uncertainty in Air Pollution and Birth Weight Study." *Statistics in Medicine*. 30(17):2187-98. PMID: 21590788.

Lum, K. And Gelfand, A.E. 2012. The Asymmetric Laplace Process for Spatial Quantile Regression (with discussion). *Bayesian Analysis*, 7, 235-276

Miranda, M.L., Anthopolos, R., Edwards, S.E. 2011. "Seasonality of Poor Pregnancy Outcomes." *North Carolina Medical Journal*. 72(6): 447-453. PMID: 22523851.

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Miranda, M.L., Edwards, S.E. 2011. "Use of Spatial Analysis to Support Environmental Health Research and Practice." *North Carolina Medical Journal*. 72(2):132-135. PMID: 21721500.

Miranda ML, Edwards SE, Chang HH, Auten RL. "Proximity to Roadways and Pregnancy Outcomes." *J. Exp Science Env Epi*. In press.

M.L. Miranda, S.E. Edwards, R. Anthopolos, D. H. Dolinsky, A. R. Kemper. 2012. "The Built Environment and Childhood Obesity in Durham, NC." *Clinical Pediatrics*. 51 (8):746-754. PMID: 22563061.

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Miranda, M.L., Edwards, S.E., Keating, M.H., Paul, C.J. 2011. "Making the Environmental Justice Grade: The Relative Burden of Air Pollution Exposure in the United States." *International Journal of Environmental Research and Public Health*. 8(6): 1755-1771. PMCID: PMC3137995.

Miranda, M.L., Edwards, S. E., Myers, E.R. 2011. "Adverse Birth Outcomes among Nulliparous versus Multiparous Women." *Public Health Reports*. 126(6): 797-805. PMID: 22043095.

Miranda, M.L., Messer, L., Kroeger, G. 2012. "Associations between the Quality of the Residential Built Environment and Pregnancy Outcomes among Women in North Carolina." *Environmental Health Perspectives*. 120(3):471-477. PMCID: PMC3295337.

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Neelon, B., Swamy, G.K., Burgette, L.F., Miranda, M.L. 2011. "A Bayesian Growth Mixture Model to Examine Maternal Hypertension and Birth Outcomes." *Statistics in Medicine*. 30(22):2721-35. PMID: 21751226.

Vinikoor-Imler, L.C., Gray, S.C., Edwards, S. E., Miranda, M.L. 2012. "The Effects of Exposure to Particulate Matter and Neighborhood Deprivation on Gestational Hypertension." *Pediatric and Perinatal Epidemiology*. 26(2): 91-100. PMID: 22324494.

Publications – In Preparation/Submission

Anthopolos, R., Messer, L.C., Kaufman, J.S., Miranda, M.L. "The built environment mediates the relationship between racial residential isolation and adverse birth outcomes in the U.S. South." In preparation.

Gray, S., Edwards, S., Miranda, M.L. "Race, Socioeconomic Status, and Air Pollution Exposure in North Carolina." In submission.

Gray, S., Edwards, S., Schultz, B., Miranda, M.L. "Assessing the Impact of Social and Environmental Factors on Birth Outcomes in North Carolina." In preparation.

Gregory, S.G., Anthopolos, R., Osgood, C., Grotegut, C.A., Miranda, M.L. "Associations of autism with augmented or induced childbirth." In preparation.

Messer, LC, Neelon, B, Anthopolos, R., Kaufman, JS. The Built Environment and Adverse Birth Outcomes: An Analysis using Biprobit Modeling to Account for Correlated Outcomes. In preparation.

Miranda, M.L., Anthopolos, R., Edwards, S.E., Kim, D. "Educational test performance according to birth weight, gestation, and prenatal smoking status." In preparation.

Neelon, B., Gelfand, A.E., Miranda, M.L. 2012. A Multivariate Spatial Mixture Model for Areal Data (submitted).

Presentations

Anthopolos, R., Messer, L., Miranda, M.L. "The Built Environment as Mediator in the Segregation-Birth Outcome Relationship." Paper presented at the American Public Health Association, Washington, DC, November 2011.

Gray, S., Edwards, S., Holland, D., Miranda, M.L. "Using Predictive Surfaces to Understand Disparities in Exposure to PM2.5 and O3 in North Carolina." Poster presented at the Eastern North American Region Conference, Washington, DC, March 2012.

Miranda, M.L., Anthopolos, R., Edwards, S., Kim, D. "Impact of Pregnancy-Related Exposures on Educational Test Scores." Paper presented at the American Public Health Association, Washington, DC, November 2011.

Miranda, M.L., Anthopolos, R., Hastings, D. "A Geospatial Analysis of the Effects of Aviation Gasoline on Childhood Blood Lead Levels. Poster presented at the Pediatric Academic Society Conference, Denver, CO, May 2011.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

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EPA Agreement Number: RD83329301-0

Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy

Project Period: Year 5

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
 - a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
 - b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
 - c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

As of 4/1/2012, 1889 women have been enrolled in the study. Women are recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information is collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.
- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 944 delivery samples collected.

All maternal data are georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Healthy Baby Study also includes an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

Genetic Data and Analysis. This project focused on genetic analysis of candidate genes, specifically those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity). To date, we have genotyped 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two candidate genes. This past year, we focused on completing the genotyping of those SNPs in the samples which had been most recently ascertained.

The bulk of our focus has been on data analysis and manuscript preparation. To that end, we detail our most recent work.

The inflammatory response influences risk for adverse birth outcomes such as low birthweight. Variability in maternal inflammatory response may be exacerbated by exposure to air pollution during pregnancy. We examined how variation in maternal inflammatory genes interacts with air pollution to affect infant birthweight (BWT) in 673 non-Hispanic black (NHB) women participating in the Healthy Pregnancy, Healthy Baby Study. Maternal residential address at enrollment was georeferenced and the distance to the nearest major roadway was calculated as

a proxy for traffic-related air pollution exposure. 105 haplotype tagging SNPs were genotyped in 20 candidate genes on maternal DNA samples. Linear regression was used to examine the relationship between SNPs and infant BWT, adjusting for infant sex, maternal age, parity, education, insurance, and smoking use. We also examined interactions between SNPs and roadway proximity. Nominal evidence for main effects on infant BWT was detected with *CR1* (rs17047661, $p=0.006$), *IL10* (rs1518111, $p=0.008$), 2 SNPs in *IL8* (rs2227538, $p=0.01$; rs2227306, $p=0.02$), *IL12B* (rs2853694, $p=0.03$), *IL6* (rs2069840, $p=0.03$) and *IL12A* (rs568408, $p=0.04$). Evidence for SNPs interacting with roadway proximity to influence BWT was detected with two SNPs in *TLR4* (rs12344353, $p=0.01$; rs5030725, $p=0.03$), two SNPs in *IL4* (rs2227282, $p=0.008$; rs2243283, $p=0.03$) and one SNP in *INFG* (rs2069714, $p=0.04$). Consistent with previous reports, genetic variation in the inflammatory response provided evidence for main effects on infant BWT among NHB women in our study. We provide the first evidence that some of these genes interact with air pollution exposure to influence infant BWT. We have met with some difficulty finding the proper publication outlet for this analysis, due to its interdisciplinary nature. Thus, after a few attempts at publication, we are now primed to submit this publication to Plos One, a journal that accepts a very broad range of topics.

Mitochondrial DNA (mtDNA) biogenesis and maintenance – a direct measure of mitochondrial load – appears to play a significant role in oxidative stress, which is the result of interference or alteration in the oxidative phosphorylation process. Recent literature has suggested that circulating maternal mtDNA levels were much higher in women with growth-restricted infants than those with normal-weight infants. Given that reactive oxygen and nitrogen species from oxidative stress have been associated with adverse pregnancy outcomes including PTB, it is plausible that mtDNA levels may be associated with gestational length or PTB. Using real-time quantitative PCR (rtPCR) to measure mtDNA content in maternal blood, we have recently completed analysis for ~ 1100 black mothers enrolled in our cohort study. Preliminary statistical analysis did not identify a clear association with mtDNA level but more detailed analysis involving environmental interactions is ongoing with intended manuscript draft completion and submission by January 2013.

Cadmium is prevalent in the environment and understudied as a developmental toxicant. We conducted an analysis of maternal cadmium exposure and leukocyte DNA methylation patterns in 17 mother-newborn pairs. A methylated cytosine-guanine (CpG) island recovery assay was used to assess over 4.6 million sites spanning 16,421 CpG islands. Exposure to cadmium and cotinine was classified for each mother-newborn pair according to maternal blood levels. Comparative methylation analysis was performed to identify genes with differential methylation levels. DNA motifs that were overrepresented among the differentially methylated genes were identified. Subsets of genes were identified that showed altered DNA methylation levels in fetal DNA associated with exposure to cadmium ($n=61$), cotinine ($n=366$), or both ($n=30$). In maternal DNA, subsets of cadmium-associated ($n=92$) and cotinine-associated ($n=134$) genes were identified. While the gene sets were largely distinct between mothers and newborns, functional similarities at the biological pathway level were identified including transcriptional regulation and apoptosis. Furthermore, conserved DNA motifs with sequence similarity to specific transcription factor binding sites were identified within the CpG islands of the gene sets. This pilot investigation provides evidence for distinct patterns of DNA methylation alterations in fetal and maternal DNA associated with exposure to cadmium. The genes with differential methylation share common motifs at the sequence level suggesting that structural commonalities in DNA sequence may affect environmentally-related DNA methylation status. This manuscript is in preparation.

The nitric oxide (NO) pathway is critical for managing oxidative damage in a variety of tissues. Reduced levels of endothelial nitric oxide synthase (NOS3) have been previously linked to pre-eclampsia, a maternal complication associated preterm birth. But also pertinent to this project is that specific polymorphisms within the inducible nitric oxide synthase (NOS2A) gene have been associated with protection to malaria, thus there may be population specific selective forces leading to differential allele frequencies for the polymorphisms in these genes. For these reasons, we hypothesized that polymorphisms within the NOS genes may differentially affect risk for preterm birth among African American mothers in our cohort. We examined 57 SNPs in the three nitric oxide synthase genes (NOS1, NOS2A and NOS3) for association with risk for preterm birth in our cohort. We identified 10 SNPs in NOS1 which were nominally associated with risk for preterm birth in our non-Hispanic white (NHW) subset of mothers. Only 1 SNP in NOS2A was nominally associated with preterm birth in our non-Hispanic black (NHB) subset of mothers. Thus, we did observe differential association with these genes and preterm birth as a function of maternal race. However, we were surprised that the effects that we observed were stronger for the NHW subset rather than the NHB subset. These data are currently being prepared for publication.

Mitochondrial DNA (mtDNA) biogenesis and maintenance – a direct measure of mitochondrial load – appears to play a significant role in oxidative stress, which is the result of interference or alteration in the oxidative phosphorylation process. Recent literature has suggested that circulating maternal mtDNA levels were much higher in women with growth-restricted infants than those with normal-weight infants. Given that reactive oxygen and nitrogen species from oxidative stress have been associated with adverse pregnancy outcomes including PTB, it is plausible that mtDNA levels may be associated with gestational length or PTB. Using real-time quantitative PCR (rtPCR) to measure mtDNA content in maternal blood, we have recently completed analysis for ~ 1100 black mothers enrolled in our cohort study. Preliminary statistical analysis did not identify a clear association with mtDNA level but more detailed analysis involving environmental interactions is ongoing with intended manuscript draft completion and submission by January 2013.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. The relationships among pregnancy intention, psychosocial health, and pregnancy outcomes have been examined, with a paper published (Maxson et al. 2011). In addition, we are examining pregnancy intention, behavioral choice, and environmental exposures. The influences of psychosocial health and smoking status have been studied, with a resulting publication (Maxson et al. 2012). In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. Cluster analysis on the personality indices were also performed, and a paper is in preparation. A paper examining the relationship between the built environment as measured through the Community Assessment Project and women's psychosocial health was published in year 5 (Messer et al. Forthcoming). Future analyses will continue with a focus on the relationships among psychosocial health, risk behaviors, chemical and non-chemical stressors, and pregnancy outcomes.

Maternal Medical Complications. Fetal health is not only individually determined, but is also influenced by maternal health and well-being. This past year, we put additional emphasis on maternal outcomes. In particular, we have begun to focus on hypertensive disorders during pregnancy. As a first step, we are trying to identify factors that affect maternal blood pressure during pregnancy. In order to make use of the entirety of blood pressure readings collected across the pregnancy, we are considering a variety of statistical approaches, including latent trajectory and sparse functional data models. Our goal is to use environmental, social and

genetic data (such as GRK5 polymorphisms) to predict these blood pressure trajectories. Ultimately we hope these predicted trajectories will aid us in predicting birth outcomes; for example, women with monotone-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves. This work has been done in collaboration with the GISSA core. We have also conducted preliminary genetic association analyses involving obesity and gestational weight gain, an issue that has come to the forefront of maternal conditions affecting not only the maternal health but also appears to have long-term effects on childhood health.

Statistical Methods Development. We developed several new statistical methodologies designed to improve analysis of the Project B data, as well as to advance statistical analysis more broadly. First, we developed and implemented methods for finding important predictors in quantile regression when there are a very large number of covariates. These methods adapted the lasso and elastic net penalties for quantile regression. We applied the methods on a mid-study sample of women to uncover a previously unreported interaction: women who smoke and who have high blood lead levels tend to have babies with lower birth weights. An article on this research has been accepted for publication by *Epidemiology* (Burgette et al. 2012).

Second, we developed and implemented methods for using factor analysis models in the context of quantile regression. The investigative team believes that many of the predictors can be grouped into underlying factors. For example, the Project B data contain several variables that measure maternal stress, and arguably we should connect birth outcomes to the underlying factor of stress rather than its individual indicators. As another example, the data contain several imperfect indicators of smoking status, and we would like to connect birth outcomes to the underlying factor of true smoking status. We implemented the model on a mid-study sample of women from Project B, and we found that the smoking factor was a strong predictor of low birth weight. An article on this research was accepted for publication in *Biometrics* (Burgette & Reiter, 2012).

Third, we developed and implemented methods for accounting for mid-study changes in measurement scales. These methods were needed because the Project B investigators switched laboratories for measuring blood levels of heavy metals midway through data collection in order to take advantage of finer measurement scales. Exploratory analysis indicated that the distributions of levels for several exposures were markedly different across the labs, so that analyses based on a simple concatenation of the two labs' data would be biased. Using the second lab scale as the standard, so that effectively measurements before the lab switch are treated as missing, we developed general purpose methodology for imputing plausible values of the missing exposure measurements. The methods are based on assumptions about the relative ranks of measurements in the two scales, e.g., a measurement in the 10th percentile in one scale should be at the 10th percentile in the other scale. We implemented this methodology on the Project B data to provide the investigative team with improved data product. An article on the methodology for this research was accepted to the *Journal of the American Statistical Association* (Burgette & Reiter. 2012).

We also developed a Bayesian growth mixture model to jointly examine the associations between longitudinal blood pressure measurements, preterm birth (PTB), and low birthweight (LBW). The model partitions women into distinct classes characterized by a mean arterial pressure (MAP) curve and joint probabilities of PTB and LBW. Each class contains a unique mixed effects model for MAP with class-specific regression coefficients and random effect covariances. To account for the high correlation between PTB and LBW, we introduce a bivariate probit model within each class to capture residual within-class dependence between

PTB and LBW. The model permits the association between PTB and LBW to vary by class, so that for some classes, PTB and LBW may be positively correlated, while for others, they may be uncorrelated or negatively correlated. We also allow maternal covariates to influence the class probabilities via a multinomial logit model. For posterior computation, we propose an efficient Markov chain Monte Carlo algorithm that combines full-conditional Gibbs and Metropolis steps. We apply our model to a sample of 1027 women enrolled in the Healthy Pregnancy, Healthy Baby Study, a prospective cohort study of host, social, and environmental contributors to disparities in pregnancy outcomes. A manuscript based on this work has been accepted for publication at *Statistics in Medicine* (Neelon et al. 2011).

We also focused statistical methods development on the genetic data. The first statistical innovation involving the genetic data is the adverse sub-population regression (ASPR) for multivariate outcomes with high dimensional predictors. The ASPR is a two component latent class model, with the dominant component corresponding to (presumed) healthy individuals and the risk of falling in the minority component characterized via a logistic regression. The logistic regression model is designed to accommodate high-dimensional predictors, as occur in studies with a large number of gene by environment interactions, through use of a flexible nonparametric multiple shrinkage approach. The Gibbs sampler is developed for posterior computation. The method was evaluated with the Project B data and has been published in *Statistics in Medicine* (Zhu et al. 2012).

As described in the previous progress report, one of the statistical innovations that we have been working on is the improvement of methodologies for admixture mapping. To that end, we developed a generalized admixture mapping (GLEAM) approach, a flexible and powerful regression method for both quantitative and qualitative traits, which is able to test for association between the trait and local ancestries in multiple loci simultaneously and adjust for covariates. The new method is based on the generalized linear model and utilizes a quadratic normal moment prior to incorporate admixture prior information. Through simulation, we demonstrated that GLEAM achieves lower type I error rate and higher power than existing methods both for qualitative traits and more significantly for quantitative traits. This work is currently under review for publication.

Collaborations with other SCEDDBO Components

The collaborative efforts across the SCEDDBO components have continued to increase over the past year. The entire SCEDDBO team prioritized air pollution as one of the primary environmental contaminants to be examined across projects. This has involved significant discussions between members of Project B with members in Project A to construct viable markers of air pollution, including proximity to major roadways, and NATA data. Project B continues to consult with Project C to make more biological synergies across the two projects. Project C introduced a nest-deprivation model into the ongoing animal experiments in an attempt to better replicate the more complex psycho-social stressors experienced by the mothers in Project B. And finally, the statistical team for the GISSA has worked hard to develop more innovative statistical approaches to disentangling the complex web of interactions that are driving the birth outcomes. These innovations have been motivated by specific questions across all three projects.

Future Activities

In the next year, we will focus on data analysis and further statistical methods innovation. Our primary interest is in bringing these two pieces together. The statistical methods innovation is driven by the needs of our data analysis and thus will continue to explore means to reduce the dimensionality of the genetic and other data, as well as impute missing data. Our overall goal is

to identify complex interactions amongst the three sides of the triangle we hypothesize influence pregnancy outcomes: host, social, and environmental contributors. As a direct result of this focus on data analysis, we anticipate preparing and publishing several manuscripts in the next year. With the data collection complete, we will be well-positioned to examine and identify combinations of factors that lead to health disparities in birth outcomes. We are particularly interested in identifying chemical and non-chemical environmental risk factors given that they are actionable to improve birth outcomes.

Publications

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Publications – In Preparation/Submission

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Presentations

Maxson, P., Messer, L., and Miranda, M.L. "The Built Environment and Women's Psychosocial Health." Oral presentation at the American Public Health Association Annual Meeting, Washington, D.C., November 2011.

Maxson, P., Edwards, S.E., and Miranda, M.L. "Environmental Exposures, Pregnancy Intention, and Behavioral Choice." Oral presentation at the American Public Health Association

Annual Meeting, Washington, D.C., November 2011.

Supplemental Keywords

Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2011 – 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Richard L. Auten (PI), W. Michael Foster

Project Period: Year 5

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments

1. For Aim 4, we have determined that fetal, not maternal Tlr4 is required for effects of maternal diesel exhaust (or diesel particle instillation) exposure on the induction of fetal pro-inflammatory cytokines in fetal lung, brain, and in placenta. Furthermore, we have determined that the maternal pulmonary inflammatory response to instilled diesel exhaust is not dependent on maternal innate immunity: Tlr4^{-/-} dams and wild-type dams had the same response. Pregnancy, as expected, dampened the inflammatory response, but this was not dependent on Tlr4.
2. Studies in collaboration with Dr. John Hollingsworth have identified a number of altered methylation sites in sensitive molecular pathways relevant to inflammation that are present in macrophages from the F3 generation born after maternal diesel inhalation/instillation.
3. Our studies on the neural contribution of persistent airway hyperreactivity in newborn mice exposed to environmentally relevant concentrations of ozone have shown that the muscarinic receptor pathway is unaffected, and that the effects are likely relevant to alterations in airway epithelial integrity, since the ozone effects on airway mechanics are apparent with inhaled methacholine challenge, but not apparent with intravenous acetylcholine challenge. The persistence of the epithelial impairment into adulthood well beyond recovery from the intermittent sub-chronic neonatal/juvenile exposures is highly relevant to the potential contribution to susceptibility in adults, which we are now evaluating.

We are also examining the afferent neural plasticity in ozone exposed newborns as a potential contributor in collaboration with Dr. David Jacoby at Oregon Health Sciences University. Once the epithelial permeability studies are finalized, we will submit the manuscript.

4. We have tested the contribution of fetal inflammation provoked by maternal diesel inhalation to susceptibility to obesity in adult mice. Diesel exposure of pregnant dams produced obese male offspring reared on a normal diet. If mice were given a high-fat diet, mice born to diesel -exposed dams had more obesity, insulin resistance, and males had higher evidence of anxiety (see manuscripts below).

Collaborations with other SCEDDBO Components

Assessment of roadway proximity effects on birth outcomes (COTC, Project A). Assessment of innate immunity role in maternal-fetal inflammatory responses to environmental exposures (Project B)

Future Activities

1. Delineation of the epigenetic mechanisms that underlie the inter-generational burden of perinatal exposure to atmospheric pollutants on juvenile and adult health, in the context of post-natal co-exposures to adverse diet, air pollutants, inflammatory challenges.
2. Identification of the mechanisms of interaction between co-exposure agents during perinatal life that affect respiratory and cognitive development during juvenile development.

Publications

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Bolton JL, Smith SH, Huff NC, Gilmour MI, Foster WM, Auten RL, Bilbo SD. "Perinatal Air Pollution Exposure Induces Neuroinflammation and Predisposes Offspring to Weight Gain in Adulthood in a Sex-specific Manner." *FASEB J*. In press.

Miranda ML, Edwards SE, Chang HH, Auten RL. "Proximity to Roadways and Pregnancy Outcomes." *J. Exp Science Env Epi*. In press.

Presentations

Auten RL, Duke University Integrated Toxicology Environmental Health Program Seminar "Air Pollution Exposure in Pregnancy Effects on Respiratory Function in Offspring: Innate Immunity as Gateway" February 17, 2012.

Auten RL, Potts EN, Mason SN, Hollingsworth, JW, Bolton JL, Bilbo SD, Foster WM. "Maternal Diesel Inhalation Augments Fetal Pulmonary Inflammation and Chronic Postnatal O₃-Induced Airway Hyperreactivity via Toll-like Receptor 4 (TLR4)" American Thoracic Society International Conference, May 23, 2012, San Francisco.

Huff NC, Bolton JL, Mistry RS, Smith SH, Auten RL, Bilbo SD. "Effects of Combined Early-life Social and Environmental Stressors on Affect Cognition and Brain Cytokine Expression." Society for Neuroscience, Washington DC November 12, 2011.

Supplemental Keywords neuroinflammation,

Title of Project/Core: Community Outreach and Translation Core

Period covered by the report: 5/1/2011 – 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Pamela Maxson (PI)

Project Period: Year 5

Objectives of Research

The central objective of the Community Outreach and Translation Core (COTC) is to create, implement, and assess strategies to translate and apply the findings of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) into relevant information for women of childbearing age, families, community groups, policy makers, and health care professionals. The COTC conducts environmental health outreach and education directed at low income and minority women and their children; enhances the capacity of disadvantaged communities to understand threats posed by environmental contaminants and non-chemical stressors; and provides a bridge between campus research, communities and policy makers. The specific aims of the COTC are:

1. Support the community-based neighborhood assessment being undertaken as part of Research Projects A and B;
2. Partner with nursing programs at Duke-affiliated hospitals to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes;
3. Develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency;
4. Deliver training to local health department personnel focused on environmental factors related to maternal health and pregnancy outcomes;
5. Participate in regional, state and federal policy dialogues to provide decision makers with policy-relevant science-based information concerning environmental exposures and health disparities related to maternal and child health and well-being; and
6. Increase awareness of maternal health and health disparities by facilitating bi-directional exchanges between Center investigators, community members, public health advocacy groups, and policy makers.

Progress Report/Summary of Accomplishments

The overall goals for COTC in year 5 were to continue to expand communication and translation efforts to specific audiences. With a communication strategy in place, the COTC utilized various communication tools appropriate to a variety of audiences. Collaboration with researchers and

groups external to SCEDDBO continued to evolve and the COTC welcomed and responded to requests for environmental health information from community groups and the general public.

The second wave of the Community Assessment Project (CAP) was completed in year 5, expanding the geographic area so it included roughly 30,700 tax parcels. This second phase captured 65% of the physical addresses for participants in the Project B cohort, providing a detailed characterization of the local neighborhood environment for a significant subset of participants. Built environment data were combined with Durham crime data and tax assessor data. In collaboration with the GISSA Core, CAP data were summarized into seven Neighborhood Health Indices. These indices have been linked to outcomes from Projects A and B. Our collaboration with community partners at all stages of the tool development, data collection, and dissemination of results provides a model for engaging the community in an active research program. The COTC will continue to disseminate the CAP results to multiple audiences (community members, public health professionals, and government officials) through publication of a descriptive report, creation of web-based resources, and in-person presentations

Specific Aim 2 of the COTC is to partner with nursing programs to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes. Implementing activities to address this Specific Aim continued as a focus of COTC efforts in Year 5. A comprehensive project was designed to develop environmental health curricula for nursing students, nursing faculty, and practicing nurses. Supplemental funding from EPA's Environmental Education Grant Program has enabled collaborations with the Ecology Center in Ann Arbor, MI to produce this curriculum.

COTC staff continues to collaborate with a variety of regional, state, and federal advisory groups including the American Lung Association Advisory Group, the Durham County Health Department Community Health Assessment Working Group, and the Obesity and Chronic Disease Committee of the Partnership for a Healthy Durham. In addition, SCEDDBO Director Marie Lynn Miranda serves on the EPA's Children's Health Protections Advisory Committee (CHPAC). The CHPAC is a federal advisory committee established in 1998 to provide independent advice to the EPA Administrator on regulations, research, and communications issues relevant to children's environmental health.

Collaborations with other SCEDDBO Components

COTC staff continues to meet monthly with the SCEDDBO investigators to keep apprised of research developments and findings, translation opportunities, and scientific outreach activities (e.g., meetings, presentations and manuscripts) of the SCEDDBO investigators. The COTC staff also provides the investigators with updates on COTC activities and opportunities to participate in outreach activities. During Year 5, as part of the communication strategy, COTC staff received a periodic update from each SCEDDBO investigator detailing any presentations, conferences, or other issues or occasions that might constitute a research translation opportunity. These regular and frequent communications enable COTC staff to keep abreast of research progress, update the website, and plan for translation efforts.

External Collaborations

The COTC has developed a wide and diverse network of collaborators among federal, state and local agencies, universities and community groups. Activities with these diverse partners cover

a broad spectrum of children's environmental health issues, ranging from birth outcomes to lead poisoning prevention, environmental exposures, and obesity.

COTC staff has developed working relationships with scientists at the U.S. EPA representing a wide variety of disciplines. These relationships have allowed for exchange of research findings and data in a number of areas including distance-to-roadway analyses, air pollution impacts on birth outcomes, community engagement, and using GIS for environmental justice analysis. In terms of formal meetings, activities with multiple state and local agencies continue to cover a wide variety of topics including the impact of the built environment on obesity and pregnancy outcomes, mapping environmental exposures and built environment variables, as well as other topics related to school-aged children. The COTC is actively working with staff at numerous state and local offices. At the state government level these offices include the Senior Advisor for Healthy Schools, the Women's Health Branch, the Nutrition Services Branch, and the Office of Healthy Carolinians. Activities with county health departments and non-profit organizations ranged from GIS training and fulfilling mapping requests to serving on advisory groups (for example Durham County's Community Health Assessment Working Group).

For the 4th consecutive year, COTC investigators mentored students in the "Break the Cycle" project sponsored by the Region 4 of the U.S. EPA, Emory University and the Southeast Pediatric Environmental Health Specialty Unit. The selected students presented the built environment data from our Community Assessment Project and its relationship with psychosocial health during pregnancy and perinatal exposure to air pollution and its effects on behavioral outcomes using a mouse model. The conference was held in Atlanta, GA, in May 2011. Dr. Pamela Maxson accompanied the students as their mentor. In addition, Dr. Maxson gave the keynote address at the conference.

Finally, the COTC continues to respond with detailed information to numerous requests from private citizens about a variety of environmental health concerns. These requests were received through both the CEHI toll-free number and via the CEHI website.

Future Activities

During the no-cost extension, the COTC will continue to expand communication and translation efforts to specific audiences. By participating in the design, planning, and execution of the Durham County Community Health Assessment, we hope to gain additional insight into community health and information needs. We will disseminate the findings of the second wave of the Community Assessment Project to community groups, government officials, and other stakeholders in North Carolina and Michigan. We will also continue our efforts to incorporate environmental health topics into continuing nursing education and sustain established collaborations with researchers within and external to SCEDDBO.

Publications

Dadabhoy, F., Maxson, P., and Auten, R. 2012. "Perinatal Exposure to Air Pollutants has Adverse Effects on Behavioral Outcomes in Mice." *International Journal of Disability in Human Development* 11(4).

Gruber, A. and Maxson, P. 2012. "Disparities in Psychosocial Health and the Built Environment during Pregnancy." *International Journal of Disability in Human Development* 11(4).

Maxson, P. 2012. "Together We Can Break the Cycle." *International Journal of Disability in Human Development* 11(4).

Publications – In Preparation/Submission

Kroeger G.L., Messer L., Edwards S.E., and Miranda M.L. "A Novel Tool for Assessing and Summarizing the Built Environment." *International Journal of Health Geographics*. In submission.

Presentations

Dadabhoy, F., Maxson, P., and Auten, R. 2012. "Perinatal Exposure to Air Pollutants has Adverse Effects on Behavioral Outcomes in Mice." Break the Cycle Conference. Emory University, Atlanta, GA. May 2011.

Gruber, A. and Maxson, P. 2012. "Disparities in Psychosocial Health and the Built Environment during Pregnancy." Break the Cycle Conference. Emory University, Atlanta, GA. May 2011.

Maxson, P. "Breaking the Cycle – a Multilayer Approach." Invited Keynote, Break the Cycle Conference. Emory University, Atlanta, GA. May 2011.

Maxson, P. "Disparities in Environmental Exposures." Invited talk, Addressing Prenatal Environmental Health Effects on Mother and Fetus, A Workshop Hosted by Southeast Pediatric Environmental Health Specialty Unit and Institute for the Study of Disadvantage and Disability. Centers for Disease Control, Atlanta, GA. May 2011.

Supplemental Keywords

Risk communication, outreach, translation, participatory research, built environment

Geographic Information System and Statistical Analysis Core

Period covered by the report: 5/1/2011 – 4/30/2012

EPA Agreement Number: RD83329301-0

Investigators: Alan Gelfand (PI), Allison Ashley-Koch, Marie Lynn Miranda, Jerome Reiter

Project Period: Year 5

Objectives of Research

The overall objective of the GIS and Statistical Analysis Core is to **support spatial and quantitative analysis needs of the Center research projects, as well as the Community Outreach and Translation Core**. Our specific aims include:

1. Providing support for the development of environmental and social data layers needed to implement data analyses required for the research projects and the Community Outreach and Translation Core;

2. Providing statistical analysis, advice, and consulting on the broad range of statistical issues that arise in conjunction with the research projects, with a particular emphasis on data reduction methods and modeling spatial and spatio-temporal data within a Bayesian framework; and,
3. Providing analysis for the unique needs of genetic data arising from the clinical and animal studies of the center.

This support core facilitates the development of innovative quantitative methodology for children's environmental health research associated with the projects and cores. Equally important, it will enhance substantive collaboration between statisticians and scientists involved in the research projects yielding improved analyses of research core data, as well as novel statistical modeling.

Progress Report/Summary of Accomplishments

During the fifth year of the project, the GISSA Core has worked to build the foundation for a spatially and temporally linked data architecture for maternal and child health outcomes from the prenatal period to early childhood. The central objective is to track mothers and offspring in their residential environments at varying time slices. While capitalizing on the extensive data warehouse that we have assembled since the Center's inception, we have continued to integrate data layers into the architecture such as metrics from the EPA's Air Quality System, National-Scale Air Toxics Assessment, and in-house constructed road proximity measures, in addition to the most recently available years of North Carolina statewide administrative data on births, educational outcomes, and blood lead levels. Based on linking methods described in the previous reporting period, the unique individual-level identifying record now enables connections across multiple administrative databases on births, blood lead surveillance, deaths, and educational outcomes. These datasets can each be examined separately and in various combinations according to the master linking file.

Moreover, with the completion of participant recruitment in Project B in August 2011, GISSA staff has focused on data quality control/quality assurance, along with finalizing the project analysis dataset and planning related studies with the participants. All of the participants have been integrated into a geographic information system with information on environmental exposures, factors of the built environment, and standard demographic data. To date, we have genotyped 1600 blood samples from pregnant women for 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes, primarily involved in either metabolism of heavy metals or immune response. In addition, we have generated the Illumina African American Admixture Chip on 1016 NHB women. With these data now available, we have begun statistical analysis looking at environmental and genetic contributions and interactions to pregnancy outcomes. These results are discussed in the Project B report. We anticipate further genotyping and statistical analysis in the coming year.

The GISSA Core has continued to provide innovative statistical support to each of the Projects. In Project A, the GISSA Core has provided statistical methods development to obtain unbiased estimates of the effect of air pollution exposure on birth outcomes (Chang et al. 2012) and address measurement issues in aggregated estimates of ambient exposure to air pollution (Berrocal et al. 2012; Gray et al. 2011; Berrocal et al. 2011). The GISSA Core marked a second publication on multiple imputation in Project B. This work extends previously developed imputation methods (Burgette et al. 2012) to handle inconsistent laboratory measurements (Burgette et al 2012).

In support of both Projects A and B, the GISSA Core has developed quantile regression techniques to examine the effect of risk factors of interest at varying quantiles along the outcome distribution, rather than limiting analyses to mean effects. As a continuation of the Center's work on joint outcome modeling (Lum & Gelfand, 2012; Burgette et al. 2011; Burgette et al. 2012), GISSA Core has also developed multivariate (Neelon et al. 2011) modeling techniques to better understand individual and shared risk factors of related health outcomes, in addition to capturing geographic variation in disease risk through spatial methods.

Collaborations with other SCEDDBO Components

By its nature, the GISSA Core is highly involved in collaborations across all Center components. On an ongoing basis, we work with the investigators of Project A and Project B to determine the relevant spatial and temporal data layers for upcoming analyses. We also remain actively involved in analysis planning in order to identify opportunities for statistical methods development. Overarching the Center, the GISSA Core is tasked with determining synergistic research areas across projects.

Future Activities

We will continue developing and expanding the geospatial data warehouse that supports analysis among various projects. The GIS team will continue working with investigators in Projects A and B to identify additional environmental layers to integrate into our data architecture. With the construction of the spatio-temporal data architecture, we will plan analyses that leverage the spatial and longitudinal nature of the data, focusing on the quantile and multivariate approaches already developed by our team.

We will continue analyses on approximately 1,600 Project B participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity. We will also continue to generate imputed datasets based on the methodology developed by the GISSA Core, in order to handle missing data and error in laboratory measurements.

Project B has completed enrollment, but maternal blood samples will continue to be analyzed for genetic and gene x environment associations with adverse birth outcomes. Additional genotyping will involve genes in the maternal stress response and vascular/endothelial cell dysfunction pathways. Statistical analysis regarding candidate gene polymorphisms has already begun and will continue in the next funding period.

Publications

All manuscripts supported by the GISSA Core are listed under the individual research projects.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling